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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,449	12/20/2001	Monica G. Marcu	213373	4132

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,449	MARCU ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17 and 22* is/are rejected.

7)☒ Claim(s) *6-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/17/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. To allow the entry of rejection(s) set forth below and to afford Applicant the opportunity to response to the instant office action, the instant office action is non-final.

Status of Claim(s)

2. Claims 2, 18-21 and 23 are cancelled. Claims 1, 3-17 and 22 are pending and under examination.

Claim Objections

3. Claims 6-7 objected to because of the following informalities: claim 6-7 depends, directly and/or indirectly, on a cancelled claim—claim 2. For the purpose of examination, claim 6 is treated as if it is written to depend on claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3-6, 12-15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (Schneider et al. Pharmacologic shifting of a balance between protein refolding and degradation mediated by Hsp90. Proc. Natl. Acad. Sci. 1996, Vol. 93, 14536-14541.) in view of Gormley et al. (Gormley et al. The interaction of coumarin antibiotics with fragments of the DNA gyrase B protein. Biochemistry, 1996,

Vol. 35, 5083-5092.) and Prodromou et al. (Prodromou et al. Identification and structural characterization of the ATP/ADP-binding site in the Hsp90 molecular chaperone. Cell, 1997, Vol. 90, 65-75.).

The claims are directed at a method of inhibiting the binding of heat shock protein (Hsp) 90 with its client protein. The method comprises contacting Hsp90 with coumarin or a coumarin derivative. The claims limit the coumarin or coumarin derivative to a coumarin antibiotic, wherein the antibiotic is chlorobiocin or coumermycin A1, and novobiocin. The claims also require that the client protein be inactive subsequent to binding of the chaperone protein to the coumarin or the coumarin derivative and degraded; the chaperone protein be in a cell and cellular proliferation is inhibited, which is later limited to cancer.

Schneider et al. teaches a method of inhibiting the binding of heat shock protein (Hsp) 90 with its client protein by contacting Hsp90 with geldanamycin, *in vivo* and in cell extract. Schneider et al. discloses that the binding of geldanamycin to Hsp90 promotes the degradation of client proteins.

Prodromou et al. discloses that the binding site for geldanamycin on Hsp90 is the same as that of the ATP-binding site on Hsp90. Prodromou et al. teaches that this binding site is homologous to the ATP-binding site of DNA gyrase B protein. Additionally, Prodromou et al. also teaches that Hsp90 is a chaperone for a wide range of client proteins, wherein the client proteins are involved in cell proliferation and tumor progression.

Gormley et al. teaches that the ATP-binding site of DNA gyrase B protein is also the binding site for coumarin and coumarin derivatives. The coumarin that Gormley et al. teaches is coumarin antibiotics, including chlorobiocin or coumermycin A1, and novobiocin.

Ergo, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Schneider, Prodromou, and Gormley et al. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teaching of Schneider, Prodromou, and Gormley et al. to modulate cell proliferation and tumor progression.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teaching of Schneider, Prodromou, and Gormley et al. because the ATP-binding site of DNA gyrase B protein, binding site for coumarin, is homologous with the ATP-binding site of Hsp90.

Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

6. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider, Prodromou, and Gormley et al., and in further view of Schulte et al. (Schulte et al. Geldanamycin-induced Destabilization of Raf-1 involves the Proteasome. Biochemical and Biophysical Research Communications, 1997, Vol. 239, 655-659.)

The claims limit the client protein to serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53.

The significance of the combined teaching of Schneider, Prodromou, and Gormley et al. is discussed above. Schneider, Prodromou, and Gormley et al. do not teach the inhibition of client proteins such as serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53 with the chaperone protein.

However, Schulte et al. teaches that the binding of geldanamycin to Hsp90 inhibits binding between Hsp90 and its client proteins--such as serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53.

As noted above, Prodromou et al. discloses that the binding site for geldanamycin on Hsp90 is the same as that of the ATP-binding site on Hsp90. Prodromou et al. teaches that this binding site is homologous to the ATP-binding site of DNA gyrase B protein. And Gormley et al. teaches that the ATP-binding site of DNA gyrase B protein is also the binding site for coumarin and coumarin derivatives. The coumarin that Gormley et al. teaches is coumarin antibiotics, including chlorobiocin or coumermycin A1, and novobiocin.

Ergo, the binding of coumarin to Hsp90 would necessarily inhibit the binding of Hsp90 to serine/threonine Raf-1, tyrosine kinase p185 erbB2, and mutant p-53. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teaching of Schneider, Prodromou, Gormley and Shulte et al. because the binding site for geldanamycin is homologous with the binding site for coumarin.

7. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Schneider, Prodromou, and Gormley et al. in further view of Hu et al. (Hu et al. Hsp90 is required for the activity of a hepatitis B virus reverse transcriptase. Proc. Natl. Acad. Sci. USA, 1996, Vol. 93, 1060-1064.).

The claims limits the client protein to hepatitis B virus reverse transcriptase, and whereupon hepatitis B virus is inhibited.

The significance of the combined teaching of Schneider, Prodromou, and Gormley et al. is discussed above.

Schneider, Prodromou, and Gormley et al. do not teach hepatitis B virus reverse transcriptase, whereupon the virus is inhibited.

However, Hu et al. teaches that Hsp90 is required for the activity of hepatitis B virus reverse transcriptase. Hu et al. teaches that reverse transcription in the virus is initiated by a protein-priming mechanism, wherein the viral encoded reverse transcriptase binds to a short RNA sequence and initiates DNA synthesis *de novo* by using a tyrosine residue within the polymerase polypeptide as the primer. Hu et al. also teaches that polymerase activation is dependent on ATP hydrolysis. Thus, without polymerase activation, the virus cannot replicate.

Gormley et al. teaches that ATP-hydrolysis is inhibited by binding coumarin and its derivatives to the ATP-binding domain of gyrase B protein.

Prodromou et al. teaches that the ATP-binding domain of gyrase B protein and ATP-binding domain of Hsp90 are homologous to one another.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Schneider, Prodromou, Gormley et al. and Hu et al. to inhibit hepatitis B viral replication.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because polymerase activation is dependent on ATP hydrolysis, which is inhibited by binding coumarin and its derivatives to the ATP-binding domain of gyrase B protein, which is homologous to ATP-binding domain of Hsp90.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 1, 8-15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Omarbasha et al. (Omarbasha et al. Effect of coumarin on the Normal Rat Prostate and on the R-3327H prostatic adenocarcinoma. Cancer Research, 1989, Vol. 49, 3045-3049.) as evidenced by Prodromou et al.

The claims are directed to a method of inhibiting the binding of heat shock protein (Hsp) 90 with its client protein. The method comprises contacting Hsp90 with coumarin. The claims later define the client proteins to include a tyrosine or serine/threonine kinase--which is later limited to tyrosine kinase $p185^{erbB2}$, serine/threonine kinase Raf-1, and

mutated p53. The claims also require that the client protein be inactive subsequent to binding of the chaperone protein to the coumarin or the coumarin derivative and degraded; Hsp90 in a cell and cellular proliferation is inhibited, wherein the cellular proliferation is cancer. The claims also require that the method be performed in vivo.

Omarbasha et al. teaches a method of inhibiting the binding of Hsp90 with its client protein, by contacting Hsp90 with coumarin for the following reasons: Omarbasha et al. teaches the administration of coumarin to mice that are infected with a tumor. Omarbasha et al. notes that coumarin contributes to the decrease in the size of the tumor. Omarbasha et al. also notes that coumarin is worthy of further consideration as an agent for use in controlling normal and abnormal growth.

While Omarbasha et al. did not attribute the noted activities to the binding of coumarin to Hsp90; however, it is well known in the art that Hsp90 acts as specific chaperone for a wide range of proteins, including those involved in cell proliferation and tumor progression, as noted by Prodromou et al. Thus, combined with this knowledge, it is determined that the coumarin administered by Omarbasha et al. would necessarily bind to Hsp90. The binding of coumarin to Hsp90 would necessarily inhibit the binding of client proteins--such as tyrosine kinase $p185^{erbB2}$, serine/threonine kinase Raf-1, and mutated p53, to Hsp90 by blocking the binding of nucleotides to Hsp90, as noted by Prodromou et al. Ergo, Omarbasha et al. teaches a method of inhibiting the binding of Hsp90 with its client protein by contacting Hsp90 with coumarin, in vivo. Therefore, Omarbasha et al. anticipates the claimed invention.

10. Claim 1, 3, 5-15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Eder et al. (Eder et al. Effect of novobiocin on the antitumor activity and tumor cell and bone marrow survivals of three alkylating agents. Cancer Research, 1989, Vol. 49, Issue 3, 595-598.), as evidenced by Prodromou et al.

The significance of claims 1, 8-15 and 22 are discussed above. Claims 3 and 5-7 further limits coumarin to a coumarin antibiotic--novobiocin, and requires the novobiocin to bind to a carboxyl-terminal region of Hsp90.

Eder et al. teaches a method of inhibiting the binding of Hsp90 with its client protein, by contacting Hsp90 with novobiocin for the following reasons:

Eder et al. teaches the administration of novobiocin to mice that are infected with a tumor. Eder et al. notes that Novobiocin increases the rate in which tumor cells are killed.

While Eder et al. did not attribute the noted activities to the binding of Novobiocin to Hsp90; however, it is well known in the art that Hsp90 acts as specific chaperone for a wide range of proteins, including those involved in cell proliferation and tumor progression, as noted by Prodromou et al. Thus, combined with this knowledge, it is determined that the coumarin administered by Eder et al. would necessarily bind to Hsp90. The binding of coumarin to Hsp90 would necessarily inhibit the binding of client proteins to Hsp90, by blocking the binding of nucleotides to Hsp90, as noted by Prodromou et al. Additionally, while Eder et al. does not disclose on the location in which novobiocin binds. However, novobiocin would necessarily bind to the carboxyl terminal region of Hsp90 in order to yield the noted activity, increase in the rate at which tumor

cells are killed. Ergo, Eder et al. teaches a method of inhibiting the binding of Hsp90 with its client protein by contacting Hsp90 with coumarin, in vivo. Therefore, Eder et al. anticipates the claimed invention.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E.Le

PRIMARY EXAMINER
ART UNIT 1648